REMARKS/ARGUMENTS

Request for Continued Examination

Applicants file concurrently herewith a Request for Continued Examination (RCE) under 37 C.F.R. § 1.114. The instant paper is Applicants' required submission under 37 C.F.R. § 1.114 to accompany the RCE.

The Objection to the Specification Should Be Withdrawn

The specification has been objected to for containing an embedded hyperlink and/or other form of browser executable code in paragraph 89.

Applicants have amended paragraph 89 of the specification to replace the recitation, "www.neb.com/neb/inteins.html" with the following citation for InBase, The Intein Database and Registry: --Perler, F.B., 2002, InBase, the Intein Database, *Nucleic Acids Res.* 30, 383-384--. Base, The Intein Database and Registry, is the database that has the hyperlink, "http://www.neb.com/neb/inteins.html". This amendment to the specification does not introduce new matter because Applicants are merely providing an alternative citation for InBase, The Intein Database and Registry, to replace the citation "http:// www.neb.com/neb/inteins.html".

In view of the amendment to the specification, the objection to the specification should be withdrawn.

Status of the claims

Claims 1-5, 11-14, 17, 18, 23, 25-27, and 29-31 stand rejected. Claims 6-10, 15, 16, 19-22, 24, 28, and 32-34 have been previously cancelled.

Applicants have amended claims 1 and 27 as described in detail below.

Applicants have amended claim 1 at part (b) to recite replace the first occurrence of the indefinite article "a" with --the-- to point out more distinctly that Applicants are referring to "the protein" recited in part (a). In the interest of expediting prosecution of the instant application, Applicants have amended claim 1 at part (b) to limit the polypeptide to a site-specific recombinase or an integrase, at subpart (i) to limit the protein portion to a domain of a viral movement protein or a domain of a viral coat protein, and at subpart (ii) to limit the modifying activity to a DNA modifying activity and to limit the segment to a site-specific recombinase or an integrase. These amendments are fully supported by the Applicants' original disclosure and claims and thus, do not introduce new matter.

Applicants have also amended claim 27 in the interest of expediting prosecution of the instant application. In particular, Applicants have amended claim 27 at part (b) to limit the protein portion to a domain of a viral movement protein or a domain of a viral coat protein, and at part (c) to limit the modifying activity to a DNA modifying activity, to limit the segment to a site-specific recombinase or an integrase, and to delete the recitation "or said protein has a segment being a transcription factor inducing transcription of said heterologous nucleic acid,". These amendments are fully supported by the Applicants' original disclosure and claims and thus, do not introduce new matter.

Applicants expressly reserve the right to file continuing applications or take such other appropriate measures deemed necessary to protect the subject matter of their original claims and disclosure.

No new matter has been added by way of amendment of the claims.

Claims 1-5, 11-14, 17, 18, 23, 25-27, and 29-31 are pending.

Reexamination and reconsideration of the application as amended are respectfully requested in view of the following remarks.

The Rejections of the Claims Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn

Claims 1-5, 11-14, 17, 18, 23, 25-27, and 29-31 remain rejected under 35 U.S.C. § 112, first paragraph. Claims 1 and 27 have been amended. This rejection is respectfully traversed.

Enablement

Claims 1-5, 11-14, 17, 18, 23, 25-27, and 29-31 remain rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with enablement requirement for the reasons of record in the Office Action mailed April 15, 2008 and for additional reasons set forth in the instant Office Action mailed January 5, 2009.

The Examiner continues to acknowledge that the specification provides guidance for the transformation of *Nicotiana* plants with provectors comprising the NPTII gene, the 5' end of TMV, a movement protein and a viral coat protein, and the introduction of integrase using the VirE2 protein system for translocation of the polypeptide into the cell. The Examiner, however, continues to allege that the specification does not provide sufficient guidance for translocation of polypeptides into the cell using any other system or for any other genes functioning as predicted other than NPTII, GUS, and the Green Fluorescent Protein.

Applicants continue to respectfully disagree with this position of the Examiner for the reasons of record as stated in their response filed October 14, 2008, which are not restated herein for the sake of brevity but incorporated herein by reference. In the interest of expediting examination of the instant application and not to limit the scope of their claimed invention, Applicants have amended claims 1 and 27. Applicants earnestly believe that amended claims 1

and 27 and their respective dependent claims are fully enabled by the specification so as to provide sufficient guidance for a person having ordinary skill in the art to make and use their claimed invention.

Amended claim 1 defines that the multi-cellular organism is plant or part thereof, that the plant or part thereof contains a heterologous nucleic acid encoding a protein and that causing the expression of the protein from the heterologous nucleic acid involves delivering a polypeptide to the multi-cellular plant organism or part thereof, said polypeptide rendering said heterologous nucleic acid expressible, *said polypeptide being selected from the group consisting of a site-specific recombinase and* an *integrase*. Furthermore, the protein is specified as: containing a protein portion enabling leaving a cell and entering other cells of said multi-cellular organism or a part thereof, wherein *said protein portion is a domain of a viral movement protein or a domain of a viral coat protein*; being capable of causing expression of said protein in cells containing said heterologous nucleic acid by a DNA modifying activity of a segment of said protein, *said segment being selected from the group consisting of a site-specific recombinase and an integrase*; and optionally being capable of controlling a cellular process of interest. Thus, the protein defined by amended claim 1 is a *fusion protein comprising a protein portion and a segment*, wherein the protein portion is a domain of a viral movement or coat protein that enables leaving a cell and entering other cells of said multi-cellular organism or a part thereof and wherein the segment of the fusion protein has a DNA modifying activity selected from the group consisting of a site-specific recombinase and an integrase.

Similarly, amended claim 27 defines that the multi-cellular organism is plant or part thereof; that the protein contains a protein portion enabling said protein of leaving a cell and entering other cells of said multi-cellular organism or a part thereof, wherein *said protein portion is a domain of a viral movement protein or a domain of a viral coat protein*; that the protein has a segment having a DNA modifying activity, *said segment being selected from the group consisting of a site-specific recombinase and an integrase*; and that the heterologous nucleic acid optionally adapted for controlling a cellular process of interest. Thus, the protein defined by

amended claim 27 is a *fusion protein comprising a protein portion and a segment*, wherein the protein portion is a domain of a viral movement or coat protein that enables leaving a cell and entering other cells of said multi-cellular organism or a part thereof and wherein the segment of the fusion protein has a DNA modifying activity selected from the group consisting of a site-specific recombinase and an integrase.

In view of the amendments and above remarks, it is apparent that those of skill in the art would be able to practice the present claims without undue experimentation. Accordingly, the enablement rejection of the claims should be withdrawn.

Written Description

Claims 1-5, 11-14, 17, 18, 23, 25-27, and 29-31 remain rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement for the reasons of record in the Office Action mailed April 15, 2008 and for additional reasons set forth in the instant Office Action mailed January 5, 2009.

The Examiner has maintained the position that the claims are directed to unspecified fragments of proteins. The Examiner alleges that the amended claims encompass literally millions or billions of embodiments encompassing any transcription factor or polymerase that have not been described for causing transcription of a heterologous nucleic acid in a plant and that the sequences required for such transcription have not been described, and then concludes that the full scope of the claims is not described. The Examiner further alleges that the specification does not describe all plant or animal transcription factors or intracellular messengers that would be capable of cell-to-cell movement in a plant or what structural requirements of such factors or messengers are responsible for this function.

While Applicants continue to respectfully disagree with the Examiner's position that the specification does not provide an adequate written description of their claimed invention, Applicants have amended Applicants have amended claims 1 and 27 as described above in the interest of expediting the prosecution of the instant application.

The specification provides an adequate description of the subject matter encompassed by the amended claims to reasonably convey to a person having ordinary skill in the relevant art that Applicants had possession of the invention at the time of filing. Amended claims 1 and 27 recite a polypeptide that either has a *specified enzymatic activity selected from the group consisting of a site-specific recombinase and an integrase*. No unspecified fragments of polypeptides are recited in the amended claims. Amended claims 1 and 27 further recite that the protein contains a protein portion that is capable of enabling leaving a cell and entering other cells of said multi-cellular organism or a part thereof, wherein the protein portion is a domain of a viral movement protein or a domain of a viral coat protein. Thus, the protein portions are not drawn to unspecified fragments but rather to specific domains of viral movement and coat proteins that are capable of enabling cell-to-cell movement. Furthermore, domains of a viral movement and coat proteins that are capable of enabling cell-to-cell movement were generally known in the art at the time of the invention and are adequately described in the instant specification to reasonably convey to a person having ordinary skill in the art that, at the time the application was filed, Applicants had possession of the invention as presently claimed. Accordingly, the written description requirement of 35 U.S.C. §112, first paragraph, has been satisfied for the amended claims.

In view of the amendments and remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 112, first paragraph, for failure to comply with the written description requirement should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 102(b) Should Be Withdrawn

Claims 1-3, 5, 11-14, 17, 18, 23, 25-27, and 29-31 remain rejected under 35 U.S.C. § 102(b) as being anticipated by Hooykaas *et al.* (WO 01/89283) for the reasons of record in the Office Action mailed April 15, 2008 and for additional reasons set forth in the instant Office

Action mailed January 5, 2009.. Claims 1 and 27 have been amended as described above. This rejection is respectfully traversed.

The Examiner indicates that Hooykaas *et al.* describes a method of controlling a cellular process by providing a plant with a fusion protein in which the polypeptide is CRE, a recombinase, and a protein portion using the VirE2 system that is capable of translocating proteins across membranes and cell-to-cell movement, wherein the recombinase induces transcription of NPTII, a heterologous gene of interest.

Applicants continue to respectfully disagree with the view the claims are anticipated by Hooykaas *et al.* for the reasons of record as stated in their response filed October 14, 2008, which are not restated herein for the sake of brevity but incorporated herein by reference. In addition, Applicants submit that the Examiner appears to have confused the "polypeptide" and the "protein" as recited in claim 1. In claim 1, the protein is expressed from the heterologous nucleic acid in plant cells and fulfills features (i) to (iii) of claim 1, i.e. it is *inter alia* capable of leaving a cell and entering other cells of said plant and is capable of causing expression of the protein by a DNA modifying activity. In claim 1, the polypeptide is a site-specific recombinase or integrase and causes expression of the protein from the heterologous nucleic acid in step (b) of claim 1.

In contrast, the protein expressed in Hooykaas *et al.* is from a heterologous nucleic acid contained in the plant is the NPTII selectable marker. There is no indication that NPTII contains a protein portion enabling leaving a cell and entering other cells. Further, there is no indication in Hooykaas *et al.*, that the NPTII has a DNA modifying activity selected from a site-specific recombinase or integrase. Therefore, Hooykaas *et al.*, does not describe a process wherein a protein is expressed from a heterologous nucleic acid contained in a plant or in plant cells, wherein the protein fulfills features (i) to (iii) of amended claim 1.

Similarly, claim 27 is novel, since Hooykaas *et al.* does not disclose a plant or a part thereof containing a heterologous nucleic acid adapted as defined in items (a) to (d) of amended

claim 27. Notably, the NPTII protein expressed from a heterologous nucleic acid in Hooykaas *et al.* does not fulfill features (b) and (c) of amended claim 27.

In view of the amendments and remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 102(b) should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 1-5, 11-14, 17, 18, 23, 25-27, and 29-31 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Klimyuk *et al.* (WO 02/088369) in view of Hooykaas *et al.* (WO 01/89283) and further in view of Xu *et al.* (WO 00/71701) for the reasons of record in the Office Action mailed April 15, 2008 and for additional reasons set forth in the instant Office Action mailed January 5, 2009. Claims 1 and 27 have been amended. This rejection is respectfully traversed.

The Examiner asserts that in response to Applicants' arguments as set forth in their response filed October 14, 2008 that one cannot show non-obviousness by attacking references individually where the rejections are based on combinations for references, citing *In re Keller*, 642 F.2d 413, 108 U.S.P.Q. 871 (C.C.P.A. 1981) and *In re Merck & Co, Inc.*, 800 F.2d 1091, 231 U.S.P.Q. 375 (Fed. Cir. 1986). The Examiner failed, however, to indicate that the Federal Circuit in *In re Merck & Co, Inc.* based this position on the assumption that a reference "must be read, not in isolation, but *for what it fairly teaches* in combination with the prior art as a whole. 800 F.2d at 1097, 231 U.S.P.Q. 381 (emphasis added). Thus, one can show non-obviousness by attacking the Office's position on the teachings of an individual reference when such a position is not based on what a reference *fairly teaches*. The Examiner is respectfully reminded that the fair teachings of a reference are based on the totality of the teachings of the entire reference and not a selected portion by itself.

Furthermore, the Examiner dismisses Applicants' argument that Xu *et al.* is essentially unrelated to the invention and to Klimyuk *et al.* as well as to Hooykaas *et al.* and that a person having ordinary skill in the art would not have combined Klimyuk *et al.* with Hooykaas *et al.* Thus, the Examiner has taken the position that one cannot show non-obviousness by arguing that a reference is unrelated to one or more other references and thus, would not have been combined by a person having ordinary skill in the art with the one or more other references to make the invention. The Examiner bases this dismissal on the on the same premise (from *In re Keller* and *In re Merck & Co., Inc.*) that, one may not argue the references individually to show non-obviousness.

Applicants respectfully disagree with the position of the Examiner that *In re Keller* and *In re Merck* support the position that one cannot show non-obviousness by arguing that a particular reference is unrelated to one or more other references and thus, would not have been combined by a person having ordinary skill in the art with the one or more other references to render obvious an invention. Furthermore, Applicants respectfully invite the Examiner to state with the particularity the support in each of these cases for such a position.

Applicants continue to respectfully disagree with the position of the Office Action that the cited combination of references renders obvious their claimed invention. In their previous response, Applicants explained that Klimyuk *et al.* does not teach a method comprising expression of a protein from a heterologous nucleic acid, wherein said protein is capable of <u>both</u>

(i) leaving a cell and entering other cells of said multi-cellular organism or a part thereof, and

(ii) causing expression of said protein in cells containing said heterologous nucleic acid.

In the present Office Action, the Examiner alleges that Klimyuk *et al.* discloses both parts, "wherein the viral movement protein and cre are expressed and cre is capable of causing expression of heterologous DNA" (p. 8). In Klimyuk *et al.*, the viral movement protein and cre

are separate proteins that are not expressed from the same type of heterologous nucleic acid, but from different nucleic acids. Thus, in Klimyuk *et al.*, there is no (fusion) protein having features (i) and (ii). In the present invention, a recombinase and a movement protein are portions of the same protein, i.e. the protein of claim 1 is a fusion protein expressed from the heterologous nucleic acid.

There is no disclosure, suggestion or any indication in Klimyuk *et al.* that the cre recombinase expressed in plant cells (such as from vector pIC2721 in Example 7) has a protein portion enabling leaving a cell and entering other cells of the plant. In Klimyuk *et al.*, cre recombinase is used for catalyzing recombination between two precursor vectors. In any event, there is no indication in Klimyuk *et al.* that cre recombinase acts on a heterologous nucleic acid that encodes the cre recombinase.

The Examiner also alleges that the claims do not limit the protein to one that causes its own expression. It is pointed out that the heterologous nucleic acid recited in item (b) of claim 1 encodes the protein, since the protein is expressed from the heterologous nucleic acid. The protein thus expressed has a protein segment causing expression of said protein in cells containing said heterologous nucleic acid (item (ii)). Thus, the heterologous nucleic acid from which the protein is expressed and that causes expression of the protein, is the same type of heterologous nucleic acid.

The Examiner then turns to Hooykaas *et al.* alleging that Hooykaas *et al.* taught a fusion protein wherein one part is a movement protein and the other is a recombinase. As pointed out above, Applicants believe that the Examiner has confused the polypeptide and the protein as recited in claim 1. In Hooykaas *et al.*, the fusion protein of cre recombinase and VirE (or VirF) is not expressed from a heterologous nucleic acid in the plant. Instead, it is introduced into plant cells from *Agrobacteria*. Thus, the fusion protein of Hooykaas *et al.* is not equivalent to the protein recited in claim 1.

The invention is not obtained even if Klimyuk *et al.* and Hooykaas *et al.* were combined. If the cre-VirE fusion of Hooykaas *et al.* was used in the system of Klimyuk *et al.*, the effect of Applicants' invention would not be obtained, since neither in Klimyuk *et al.* nor in Hooykaas *et al.* does cre recombinase cause expression of the fusion protein from a heterologous nucleic acid in plant cells. Thus, little (externally provided) cre-VirE fusion would be available for efficient movement of fusion protein to neighboring cells. Instead, in the present invention, in cells reached by the fusion protein, new fusion protein can be produced from the heterologous nucleic acid, whereby efficient further movement to other cells is possible. Thus, Applicants, claimed invention provides this important advantage (i.e., efficient further movement to other cells) over the combination of Klimyuk *et al.* and Hooykaas *et al.* or the combination of Klimyuk *et al.*, Hooykaas *et al.*, and Xu *et al.*

The skilled person departing from Klimyuk *et al.* does not even have a reason to use a moving cre recombinase, since in Klimyuk *et al.* replicons are formed by the action of the recombinase. The replicon may encode a movement protein, whereby efficient cell-to-cell spread is achieved by the replicon. Cell-to-cell movement of the recombinase is therefore not necessary. Furthermore, Xu *et al.* contains no hint that would have motivated the a person having ordinary sill in the art to combine its teachings with that of Klimyuk *et al.* and/or Hooykaas *et al.* to make Applicants' claimed invention.

In summary, one of skill in the art would not find that the subject matter encompassed by the amended claims is obvious in view of the combination of Klimyuk *et al.*, Hooykaas *et al.*, and Xu *et al.* As discussed above, one of skill in the art would not have combined the teachings of Klimyuk *et al.*, Hooykaas *et al.*, and Xu *et al.* to make Applicant's invention as presently claimed. More importantly, even if the skilled person had combined the teaching of Klimyuk *et al.*, Hooykaas *et al.*, and Xu *et al.*, this combination fails to provide all of the elements of the amended claims. Therefore, the Examiner has failed to raise a *prima facie* case of obviousness under 35 U.S.C. § 103(a).

Although Applicants continue to respectfully disagree with the position of the Office Action that the cited combination of references renders obvious their claimed invention, Applicants have amended Applicants have amended claims 1 and 27 as described above in the interest of expediting the prosecution of the instant application. Applicants believe amended claims 1 and 27 and their respective dependent claims are not obvious in view of the combination of Klimyuk *et al.*, Hooykaas *et al.*, and Xu *et al.* for the reasons stated above and as well as the reasons of record in Applicants' last response to the Office.

In view of the amendments and remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 103(a) should be withdrawn.

Status of the Claims of Co-Pending Application No. 10/535,766

The pending claims of co-pending Application No. 10/535,766 (371(c) date June 22, 2005) are drawn to a method of controlling a genetically modified plant or plant cells and plants and compositions used in this method. The method comprises the steps of providing a genetically-modified plant or plant cells, wherein the plant or plant cells contain a heterologous nucleic acid encoding a first polypeptide containing or consisting of a first fragment of a protein, introducing a second polypeptide into cells of the genetically-modified plant or plant cells, wherein the second polypeptide containing a second fragment of the protein and a peptide sequence enabling the introduction of the second polypeptide into cells of the genetically-modified plant or plant cells, whereby the first fragment and the second fragment jointly generate a predetermined function of the protein only when jointly present. Claims 1, 3, 5, 7-9, 21, 23-28, and 31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Klimyuk *et al.* (WO 02/088369) in view of Hooykaas *et al.* (WO 01/89283) and further in view of Xu *et al.* (WO 00/71701).

Status of the Claims of Co-Pending Application No. 10/535,780

The pending claims of co-pending Application No. 10/535,780 (371(c) date June 22, 2005) are drawn to a method of controlling a controlling a genetically-modified plant and plants and compositions used in this method. The method comprises the steps of providing a genetically-modified plant, whereby cells of said genetically-modified plant contain a heterologous nucleic acid and whereby the genetically-modified plant is inactive with regard to a cellular process of interest, and switching on the cellular process of interest by directly introducing a polypeptide from a cell-free composition into cells containing the heterologous nucleic acid, wherein the polypeptide and said heterologous nucleic acid are mutually adapted such that the polypeptide is capable of switching on the cellular process of interest. Claims 1, 6-8, 11, 13-17, 25, 26, and 31 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Hooykaas *et al.* (WO 01/89283). Claims 1, 2, 6-8, 11, 13-22, 25-28 and 31 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Klimyuk *et al.* (WO 02/088369) in view of Hooykaas *et al.* (WO 01/89283) and further in view of Xu *et al.* (WO 00/71701).

CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §§ 102(b), 103(a), and 112, first paragraph, are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of

this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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